A Simple, Efficient, and Selective Method for Tetrahydropyranylation of Alcohols on a Solid Phase of Alumina Impregnated with Zinc Chloride

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The tetrahydropyranylation is one of the most frequently used processes to protect hydroxyl groups.[1] Because of the remarkable stability of tetrahydropyranyl ethers toward a variety of conditions, such as strongly basic media, reactions involving Grignard reagents and lithium alkyls, reduction with hydride, oxidation, oxidative alkylation, and acylation reactions etc., tetrahydropyranylation is one of the methods of choice to protect a hydroxyl group in a multistep organic synthesis.[2] A variety of reagents[1] have been developed for the tetrahydropyranylation of alcohols which include mainly protic acids (hydrochloric acid and *p*-toluenesulfonic acid), Lewis acids (BF_3-OEt_2, aluminum sulfate on silica gel,[3] pyridinium *p*-toluenesulfonate, and bis(trimethylsilyl)-sulfate), ion-exchange resins (amberlyst H-15[4] and Nafion-H[5]), clay material (montmorillonite K-10[2] and H-Y zeolite[6]) as well as other miscellaneous catalysts[7] such as DDQ,[7a] *p*-toluenesulfonates,[7] and charcoal,[7] etc. Although these methods are satisfactory for many molecules, they can have limitations when applied to complex molecules containing acid-sensitive functionalities and more than one hydroxyl group. Thus there is a need for mild and efficient alternative for protection of hydroxyl group as a THP ether. As a part of our continued efforts to utilize surface-mediated reactions for useful synthetic transformations[8] we have recently introduced a technique to tune the acidity of a Lewis acid by impregnating it in a suitable adsorbent. Thus, $ZnCl_2$ supported on alumina has been successfully employed in the Mukaiyama Michael addition of silyl enol and dienol ethers with alkyl vinyl ketone[8f,i] avoiding polymerization of methyl vinyl ketone, usually associated with reactions catalyzed by $ZnCl_2$ and other Lewis acids. We wish to disclose here another useful application of $ZnCl_2$-impregnated alumina for tetrahydropyranylation of alcohols through a simple solvent free reaction (Scheme 1).

In a typical reaction, a mixture of the alcohol and 3,4-dihydro-2*H*-pyran was added to the solid surface of alumina impregnated with anhydrous zinc chloride under stirring. After the reaction was complete, the product was isolated by simple elution of the solid mass by methylene chloride and evaporation of solvent. A wide range of hydroxy compounds were converted to the corresponding THP ethers in high yields by this procedure. The results are presented in Table 1. The reactions are reasonably fast; even the bulky molecules like *l*-menthol (entry 6) and cholesterol (entry 7) which required days to be completed by many conventional methods are found to give satisfactory yields in few hours stirring at room temperature. The reaction conditions are mild enough not to induce any isomerization of double or triple bonds during tetrahydropyranylation of allylic and propargylic alcohols (entries 8 and 9). The acid-sensitive functionalities such as ketal, methoxy, and carboxylic ester are also safe under this procedure (entries 12–15). One notable achievement of this reagent system is the selective monotetrahydropyranylation of 1,*n*-diols (entries 10 and 11), which is very difficult to achieve with common reagents.[3]

Interestingly, reactions catalyzed by zinc chloride alone in the absence of alumina in THF or on the alumina surface (dry medium) without zinc chloride are sluggish. On the other hand, when the reaction is carried out in solvent (CH_2Cl_2 or THF) under identical conditions with $ZnCl_2$-impregnated alumina the progress of tetrahydropyranylation is practically nil. Thus, a combination of the solid surface of alumina and zinc chloride with absence of solvent is essential for a satisfactory reaction. Although the precise role of the dry surface of alumina to effect this reaction so efficiently is yet to be determined, this clearly demonstrates a novel and potential facet of surface-mediated solid phase reaction.[9]

In conclusion, the present method provides a useful alternative to the preparation of tetrahydropyranyl ethers from alcohols. The notable advantages of this methodology are mild conditions (room temperature), fast reaction time (10 min to 7 h), tolerance to a wide range of functionalities, selectivity for 1,*n*-diols, no aqueous work-up, low cost (alumina can be recycled after being reactivated), and high yield (75–90%). We believe this will serve as a useful addition to modern organic synthetic methodologies.

Experimental Section

General. General informations regarding instruments and techniques used are the same as mentioned in our earlier

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Scheme 1

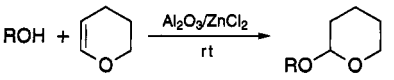
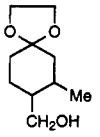
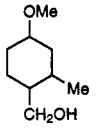
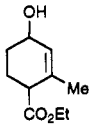
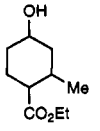


Table 1. Tetrahydropyranylation of Alcohols on the Surface of Alumina Impregnated with $ZnCl_2$

entry	alcohol	time	yield (%) of THP ethers[a]
1	*n*-hexanol	15 min	90[1u]
2	benzyl alcohol	10 min	89[2]
3	tetrahydrofurfuryl alcohol	30 min	90[11]
4	cyclohexanol	2 h	83[10,5]
5	2-propanol	2 h	82[2]
6	*l*-menthol	5.5 h	88[7d]
7	cholesterol	7 h	82[12]
8	allylic alcohol	15 min	85[2]
9	propargylic alcohol	10 min	87[4]
10	1,2-ethanediol	30 min[b]	78[3]
11	1,3-propanediol	30 min[b]	75[3]
12		30 min	84
13		30 min	80
14		4 h	80
15		3 h	83

[a] All yields refer to pure isolated products, fully characterized by IR and ^1H NMR. [b] The reaction was run at 0–5 °C.

paper.[13] Elemental analyses were performed by Mr. S. Sarkar of this laboratory.

Alumina (acidic, Brockmann activity, grade 1 for column chromatography, SRL, India) was activated by heating at 200 °C for 4 h under vacuum followed by cooling under N_2 and was used for all the reactions. (Activated alumina can be stored under N_2 for 1 week for subsequent uses without much loss of activity.) Petroleum ether refers to the fraction boiling between 60 and 80 °C.

The alcohols used for tetrahydropyranylation are mostly commercial materials and were purified by distillation or recrystallization before use. A few were obtained by standard manipulations from known carbonyl compounds.

General Procedure for Tetrahydropyranylation. Representative Procedure. Activated alumina (1.1 g, 10 times the weight of alcohol used) was stirred with a solution of anhydrous zinc chloride (150 mg, 1.1 mmol, Fluka) in THF (2 mL) for 5 min after which the excess THF was removed under reduced pressure to furnish $ZnCl_2$-impregnated alumina as a white powder. This reagent (it can be stored under nitrogen for a few days, if necessary, without loss of activity) was then added to a stirred mixture of benzyl alcohol (108 mg, 1 mmol) and 3,4-dihydro-2*H*-pyran (92 mg, 1.1 mmol), and stirring was continued at room temperature (28 °C) for 10 min (Table 1) as required for completion (monitored by TLC). The solid mass was then eluted with methylene chloride (25 mL), and the extract was evaporated to afford the crude product. This was further purified by filtering it through a short column of silica gel (eluted with petroleum ether) to produce the pure THP ether (170 mg, 89%).

The THP ethers are mostly known compounds and were characterized easily by comparison with authentic samples (IR, ^1H NMR, mp). However, spectral and analytical data of a few new compounds are given below, designated by their entries in Table 1.

12: ^1H NMR δ 0.95 (3H, d, J = 6 Hz), 1.0–2.2 (10H, m), 3.0–4.1 (8H, m with a singlet at 3.83), 4.5 (1H, broad). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.37; H, 9.54.

13: ^1H NMR δ 0.96 (3H, d, J = 6 Hz), 1.1–2.16 (14H, m), 2.83–4.0 (8H, m with a singlet at 3.3), 4.5 (1H, broad). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.31; H, 8.78.

14: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR δ 1.30 (3H, t, J = 7 Hz), 1.13–2.56 (14H, m), 3.26–3.88 (3H, m), 4.13 (2H, q, J = 7 Hz), 4.66 (1H, broad), 5.6 (1H, broad). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.28; H, 9.12.

15: IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 1.01 (3H, d, J = 6 Hz), 1.25 (3H, t, J = 7 Hz), 1.4–2.72 (14H, m), 3.10–3.38 (3H, m), 4.08 (2H, q, J = 7 Hz), 4.7 and 4.8 (1H, broad). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.45; H, 9.72.

Although the results reported in Table 1 were based on 1 mmol scale reactions, gram-scale reactions also afforded the corresponding products in analogously good yields.

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